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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/707,087	11/06/2000	Carl H. June	RPI-034CPCN	8859

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Lahive & Cockfield
28 State Street
Boston, MA 02109

EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	11

DATE MAILED: 10/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/707,087	JUNE ET AL.	
	Examiner	Art Unit	
	Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 32-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 32-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The amendment filed on July 2002 has been entered and assigned as Paper #10. Claim 1 has been amended, claims 32-46 are newly submitted, and claims 1, 32-46 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, and the rejection applies to newly submitted claims 32-46.

Applicant's amendment to claim 1 and submission of new claims has resulted in the following modification to instant grounds of rejection.

Claim 1 has been amended to embrace contacting T cells *ex vivo* with at least two agents selected from the group consisting of an anti-CD28, anti-CD3, anti-CD2 antibodies, a CD28L, IL-2, ionomycin, A23187, phorbol-12, 13-dibutyrate, lectin and a

superantigen. Given the broadest reasonable interpretation, the claims read on using any combination of two agents selected from said group. However, the specification provides numerous disclosures contradictory to itself and to the art of record.

The specification teaches that the cell viability would be greater after γ-irradiation in a medium containing anti-CD3Ig, anti-CD28Ig or combination thereof compared to the medium absent of these antibodies in example 1. Whereas in example 6, the specification teaches that bcl-X2 prevents anti-CD3 induced programmed cell death (PCD). Thus, anti-CD3Ig serves as a rescue force preventing cell death in example 1, but an apoptotic inducer in example 6. It is noteworthy that the later observation is in agreement with the art of record (US 5,691,341, column 4, lines 28-34; and US 6,303,121, column 16, lines 20-23), both cited patents teach that anti-CD3 induces apoptosis in murine and human T cells. *Kwon* (US 6,303,1210) also teaches that continued presence of anti-CD3 in cell culture would cause T cell unresponsiveness to even saturated anti-CD28, leading to irreversible cell damage (column 21, lines 9-35).

The specification teaches that IL-2 will rescue the irradiation-induced cell-death, (example 2). *Lenardo* (US 6,083,503) teaches using IL-2 to cause T cells undergo apoptosis upon re-immunization with an antigen (abstract). *Lenardo* further teaches, "A CRITICAL DETERMINANT OF THE CHOICE BETWEEN T LYMPHOCYTE PROLIFERATION OR PROGRAMMED CELL DEATH IS THE PRIOR EXPOSURE OF THESE CELLS TO IL-2", (column 1, lines 48-64). In view of such teaching, the claims do not seem to be enabled for T cells previously exposed to IL-2.

The specification contemplates, "*Superantigens capable of augmenting bcl-Xl protein level in T cells are also within the scope of the invention", "Superantigens can also be of viral origin such as retroviral superantigens*" (Specification, page 18, lines 29-33). However, *Johnson et al* (US 5,968,514) teach, "HIV INFECTION ALSO RESULTS IN THE PROGRAMMED CELL DEATH OF CD4+ T CELLS (APOPTOSIS), BOTH IN VITRO AND IN VIVO, POSSIBLY AS A RESULT OF AN HIV PROTEIN WITH SUPERANTIGEN PROPERTIES" (column 4, lines 26-44). *Lenardo* (US 6,083,503) teaches that bacterial *Staphylococcus* superantigen induces T cell PCD in mice (column 1, lines 59-64). *Lynch et al* (US 6,015,559) teach, "TNF COULD ACCOUNT FOR THE REPORTED ABILITY OF CERTAIN ANTIGENS AND SUPERANTIGENS TO CAUSE T CELL DELETION IN LPR MICE" (column 30, lines 20-26).

The specification contemplates, "*Other agents which can be employed to stimulate T cell survival include agents such as polycolonal activators that are capable of augmenting bcl-Xl protein level...include lectins such as PHA, Con A and PWM*" (Specification, page 18, lines 24-28). However, *Kwon* (US 6,303,1210) teaches using PHA as a trigger to induce PCD in T cells (columns 18 and 19). *Schlossman et al* (US 5,843,635) teach, "TREATMENT WITH ANTI-CD3 ANTIBODY, IONOMYCIN, AND/OR PHORBOL ESTER CAN INDUCE APOPTOSIS IN BOTH HUMAN AND MOUSE IMMATURE THYMOCYTES" (column 1, lines 23-28), and go on to teach, "CULTURING PBT CELLS WITH PMA-TREATED MONOCYTES IN MEDIUM CONTAINING IONOMYCIN OR PMA INCREASED THE LEVEL OF APOPTOSIS BY ALMOST 3- AND 6- FOLD, RESPECTIVELY" (column 7, lines 52-54).

In view of foregoing cited teachings, the combination of IL-2, anti-CD28, and CD28L may prevent cell death in culture, whereas the combination of rest of the agents recited in claim 1 and claim 39 may promote cell death. It is concluded in light of

numerous conflicting teachings in patents cited foregoing, the invention does not appear to be enabled absence of clarification of the contradictory evidence found in the references.

Newly submitted claims 39-46 are clearly directed to a method for protecting a T cell from cell death *in vivo*, particularly in a human subject. With regard to claim breadth, it clearly reads on a therapeutic method in humans, thus will be evaluated by that standard.

The teachings of the specification are illustrated by data obtained in cell cultures. The numerous teachings cited in the preceding paragraphs also rely mostly on *in vitro* data, which illustrate the underdeveloped state of the pertinent art. It depends on many factors directly or indirectly associated with apoptosis to determine whether a T cell would undergo apoptosis, e.g. the type and state of T cells, the prior exposure to other elements, etc. This is true for simplified *in vitro* experiments, and even more so for complicated *in vivo* experiments.

It is the general knowledge in the pertinent art, that cell culture system is a simplified model for biological study. There are many pathways that trigger PCD. In addition to T cell receptors, Fas/FasL, TNF family proteins, and downstream caspase proteases, to name a few. The protective effect of instantly claimed two agents on the T cells is unpredictable in the context of the host environment, wherein multiple factors are present. As discussed in detail in the previous Office action, it is known in general according to various *in vitro* experimentation that Bcl-X_L is associated with the resistance to growth factor-dependent cell death (*Boise et al,* Cell 1993;75:597-608), to

immune suppressant-induced and protein synthesis inhibitor-induced cell death (*Gottschalk et al*, Proc. Natl. Acad. Sci. USA). However, the art is still unpredictable with regard to particular cell types and agents that enhance Bcl-X_L levels. For example, *Boise et al* teach that six hours of stimulation with PMA and ionomycin had no effect on bcl-x mRNA expression in double-positive thymocyte populations but induced a dramatic increase in bcl-x mRNA expression in both single-positive thymocytes and peripheral blood T cells (page 603, 1st paragraph). *Gottschalk et al* teach that Cyclosporin A, FK-506, and rapamycin could prevent PCD in T-cell hybridomas and thymocytes, but induce PCD in B cells (abstract). It is generally known in the art that anti-CD28 antibodies would protect T cells from apoptosis *in vitro* (US 5,686,281, column 3, lines 51-65), however, as taught by *Roberts* and foregoing references, many other cell surface receptors, apoptotic associated molecules, environmental factors also play a role in the state of the T cells, the specification fails to teach with regard to *in vivo* aspects of the invention, the influence of other factors, the disease and the disorder that would need T cell protection, whether and how long the protective effect of *in vitro* T cell treatment would last. In view of such, the fate of treated T cells is highly unpredictable in a complicated *in vivo* environment, thus, resulting in a trial and error situation. The court has made it very clear, "COURT ERRED IN ACCEPTING IN VITRO DATA AS SUPPORT FOR CLAIMS CONTAINING IN VIVO LIMITATION". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

Thus, it is evident that the skilled practitioner in the art while acknowledge that Bcl-X_L could be one of the potential target in the prevention of T cell PCD, it is not

routine nor acceptable that any and all recited combination of molecules renders protection to T cells, or effectively doing so *in vivo*. Therefore, it is incumbent upon applicants to provide an enabling disclosure for the recited use within the specification. However, the specification fails to provide such an enabling disclosure commensurate to the scope of the claim.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving therapeutic effects, in particular for protection of T cells *in vivo*, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to *ex vivo* therapy of any and all diseases or disorders, and the breadth of the claims directed to the use of numerous combinations of therapeutic agents, whose asserted functions are contradictory within the specification and with the teachings of the cited art, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Please note that the applicant has not provided any arguments regarding the specific issues concerning the unpredictability of *in vivo* therapy raised above and in the previous rejection of record.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application

by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

(f) he did not himself invent the subject matter sought to be patented.

Claims 1, 34, 37, and 38 are under 35 U.S.C. 102(e) as being anticipated by *Thompson et al* (US 6,352,694).

The reference patent qualifies as prior art under this provision because there is one common inventor and no common assignee between the instant application and the cited patent.

The claims are drawn to a method comprising contacting T cells ex vivo with at least two agents, selected from the group consisting of an anti-CD28 antibody, an anti-CD3 antibody, or a CD28 ligand for example, wherein the T cell is a mammalian T cell, and the CD28 ligand is a B7-1 or B7-2 molecule or fragment thereof, wherein the T cells are HIV infected.

Thompson et al teach, a method comprising contacting T cells *in vitro* with an anti-CD3 antibody (step a of claims 1 and 17 of the cited patent), then an anti-CD28 antibody (step b of claim 1 of the cited patent) or a CD28 ligand selected from B7-1 or B7-2 (step b of claim 17). *Thompson et al* also teach that the T cells could be used in treating infectious disease and cancer, which embrace HIV (claims 15, 16, 31, and 32). Thus, the cited patents anticipate the instant claims.

Claim recitation "for inducing a population of T cells" or "for protecting a T cell from cell death" have not been given patentable weight in this rejection because they merely recite an intended use of the process. Please note that intended use limitations bear little weight on the determination of novelty of the invention. This is because a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of

performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

It is a general rule that merely discovering and claiming a new benefit to an old process cannot render the process again patentable. *In re Woodruff* 919 F. 2d 1575, 1577-78, 16 USPQ2d 1934, 1936-37 (Fed. Cir. 1990); *In re Swinehart*, 439 F. 2d 210, 213, 169 USPQ 226, 229 (CCPA 1971); and *Ex Parte Novitski*, 26 USPQ2d 1389, 1391 (Bd. Pat. App. & Int. 1993).

Claims 1, 34, 37, and 38 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

The reference patent qualifies as prior art under this provision because there is one common inventor and no common assignee between the instant application and the cited patent.

This application has a different inventive entity with a single common inventor as that of US Patent 6,352,694. Because claims 1, 34, and 38 of the instant application is anticipated by the claims 1, 17-19 of the cited patent, the inventive entity on the instant application appears to be unclear with regard to who is the real inventor.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 34, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Lenardo* (US 6,083,503), and in view of *Roberts* (US 5,686,281).

Lenardo teaches that blockage of IL-2 receptor (contacting IL-2 or agonist) reverses bacterial superantigen induced T cell PCD (column 1, lines 48-64), *Roberts* teaches anti-CD28 antibodies would protect T cells from apoptosis *in vitro* (column 3, lines 51-65). *Lenardo* or *Robert* does not teach to use the combination of two agents for T cell protection.

However, it would have been obvious for one skilled in the art to combine the teachings of *Lenardo and Robert* in the prevention of T cell from undergoing apoptosis in cultures with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to do so because the addition of two protecting agents would enhance the protective effect for T cells, and IL-2 is a commonly used cytokine in T cell cultures. Therefore, the claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 34, 37, and 38 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 15-19, 31, and 32 of U.S. Patent No. 6,352,694.

The reference patent qualifies as prior art under this provision because there is one common inventor and no common assignee between the instant application and the cited patent.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 34, 37, and 38 of the present application and claims 1, 15-19, 31, and 32 of the cited patent are each drawn to a method comprising the steps of contacting the T cell with two agents, i.e. anti-CD3 antibody, and anti-CD28 antibody, or a CD28 ligand, wherein the T cells are HIV infected (infectious and cancerous).

The processes of the present application and the cited patent differ one from the other in the preamble recitations, however, the recitations "for inducing a population of T cells" in the cited patent or "for protecting a T cell from cell death" in the present application are obvious variants, i.e. T cells in a healthy growing state are resistant to apoptosis. Further, the preamble recitations have not been given patentable weight because they merely recite an intended use of the process. Please note that intended use limitations bear little weight on the determination of novelty of the invention. This is it is a general rule that merely discovering and claiming a new benefit to an old process

cannot render the process again patentable. *In re Woodruff* 919 F. 2d 1575, 1577-78, 16 USPQ2d 1934, 1936-37 (Fed. Cir. 1990); *In re Swinehart*, 439 F. 2d 210, 213, 169 USPQ 226, 229 (CCPA 1971); and *Ex Parte Novitski*, 26 USPQ2d 1389, 1391 (Bd. Pat. App. & Int. 1993).

The claims of the present application additionally embrace the claims of the cited patent because the instant contacting encompasses any means of contact, whereas in the cited patent, the anti-CD3 antibody is immobilized on a solid phase surface.

Accordingly, the inventions as claimed are co-extensive.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
September 27, 2002

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER